

WHAT IS CLAIMED IS:

1. Method for the production of recombinant DNA-derived tissue plasminogen activator (tPA), a tPA variant, a Kringle 2 Serine protease molecule (K2S) or a K2S variant in prokaryotic cells, wherein said tPA, tPA variant, K2S molecule or K2S variant is secreted extracellularly as an active and correctly folded protein, characterized in that the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA or a functional derivative thereof.

2. Method according to claim 1, characterised in that said the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA which is operably linked to the nucleic acid molecule defined by the sequence TCTGAGGGAAACAGTGAC (SEQ ID NO:1) or a functional derivative thereof.

3. Method according to claim 1 or 2, characterised in that the prokaryotic cell is *E. coli*.

4. Method according to one of claims 1 to 3, characterised in that the following steps are carried out:

- a) the DNA encoding the tPA, tPA variant, K2S molecule or K2S variant is amplified by PCR;
- b) the PCR product is purified;
- c) said PCR product is inserted into a vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII in such a way that said PCR product is operably linked upstream to the DNA coding for the OmpA signal sequence and linked downstream to the DNA coding for gpIII of said vector;

- d) that a stop codon is inserted between said tPA, tPA variant, K2S molecule or K2S variant and gpIII;
- e) said vector is expressed by the prokaryotic cell;
- f) the tPA, tPA variant, K2S molecule or K2S variant is purified.

5. Method according to one of claims 1 to 4, characterised in that the vector is a phagemid vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII.

6. Method according to one of claims 1 to 5, characterised in that the vector is the pComb3HSS phagemid.

7. Method according to one of claims 1 to 6, characterised in that the DNA Sequence of OmpA linked upstream to K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCAGGCAGGCCCTCTGAGGGAAACAGTGACTGCTACTT
TGGAATGGGTAGCCTACCGTGGCACGCCAGCCTCACCGAGTCG
GGTCGCTCCTGCCCTCCCGTGGATTCCATGATCCTGATAGGCAAGG
TTTACACAGCACAGAACCCCCAGTGCCCAAGGACTGGGCCTGGGCA
AACATAATTACTGCCGAATCCTGATGGGGATGCCAAGCCCTGGT
CCACGTGTAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT
GCCCTCCTGCTCCACCTGCCCTGAGACAGTACAGCCAGCCTCAG
TTTCGCATCAAAGGAGGGCTTTCGCGACATGCCCTCCCACCCCT
GGCAGGCTGCCATTTGCCAAGCACAGGAGGTCGCCGGAGAGC
GGTCTCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCT
GCCGCCACTGCTTCCAGGAGAGGTTCCGCCACCCACCTGACGG
TGATCTGGCAGAACATACCGGGTGGCCCTGGCGAGGAGGAGC
AGAAATTGAAGTCGAAAATACATTGTCATAAGGAATTGATGA

TGACACTTACGACAATGACATTGCGCTGCAGCTGAAATCGGAT
TCGTCCCGCTGTGCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC
TTCCCCCGGGACCTGCAGCTGCCGACTGGACGGAGTGTGAGCT
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTCTATTGGAG
CGGCTGAAGGAGGCTATGTCAGACTGTACCCATCCAGCCGCTGCA
CATCACAAACATTACTTAACAGAACAGTCACCGACAACATGCTGTG
TGCTGGAGACACTGGAGCGGGGGCCCCCAGGCAAACATTGACGA
CGCCTGCCAGGGCATTCGGGAGGGCCCCCTGGTGTGTCTGAACGAT
GGCCGCATGACTTGGTGGGCATCATCAGCTGGGGCCTGGCTGTG
GACAGAAGGATGTCCCAGGTGTACACAAAGGTACCAACTACCT
AGACTGGATTGTCGTACAACATGCGACCG (SEQ ID NO:2)

8. Method according to one of claims 1 to 7, characterised in that the DNA Sequence of OmpA comprises the following sequence:

ATGAAAAAGACAGCTATCCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCCAGGCGGCC (SEQ ID NO:3)

9. Method according to one of claims 1 to 8, characterised in that the DNA Sequence of OmpA consists of the following sequence:

ATGAAAAAGACAGCTATCCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCCAGGCGGCC (SEQ ID NO:3)

10. Method according to one of claims 1 to 9, characterised in that the DNA of the tPA, tPA variant, K2S molecule or K2S variant is preceeded by a lac promotor and/or a ribosomal binding site.

11. Method according to one of claims 1 to 10, characterised in that the DNA coding for the tPA, tPA variant, K2S molecule or K2S variant is selected from the group of DNA molecules coding for at least 90% of the amino acids 87 – 527, 174 – 527, 180 – 527 or 220 – 527 of the human tissue plasminogen activator protein.

12. Method according to one of claims 5 to 11, characterised in that the DNA Sequence of K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

TCTGAGGGAAACAGTGACTGCTACTTTGGAATGGGTCAAGCCTACC
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCCTGCCTCCCGTG
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC
AGTGCCCAGGCACTGGGCCTGGGAAACATAATTACTGCCGGAATC
CTGATGGGATGCCAAGCCTGGTGCACGTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCTGCTCCACCTGCGG
CCTGAGACAGTACAGCCAGCCTCAGTTGCATCAAAGGAGGGCTC
TTCGCCACATGCCCTCCCCACCCCTGGCAGGCTGCCATCTTGCA
AGCACAGGAGGTCGCCGGAGAGCGGTTCCCTGTGCCGGGGCATAC
TCATCAGCTCTGCTGGATTCTCTGCCCCACTGCTCCAGGAG
AGGTTTCCGCCCCACCACCTGACGGTGAACGGAGGGCAAAACATACC
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTGAAGTCGAAAAAT
ACATTGTCCATAAGGAATTGATGATGACACTTACGACAATGACAT
TGCCTGCTGCACTGGATTCTGCTCCGCTGTGCCAGGAG
AGCAGCGTGGTCCGACTGTGCTCCCGCGACCTGCAGC
TGCCGGACTGACGGAGTGTGAGCTCTCGCTACGGCAAGCATG
AGGCCTTGTCTCTTCTATCGGAGCGCTGAAGGAGGCTCATGT
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTACITAAC
AGAACAGTCACCGACAACATGCTGTGCTGGAGACACTCGGAGC
GGCGGGCCCCCAGGCAAATTGACAGCAGCCCTGCCAGGGCGATTG
GGAGGCCCCCTGGTGTGCTGAACGATGCCGCTGACTTTGGTGG
GCATCATCAGCTGGGCCTGGCTGTGGACAGAAGGATGTCCCG
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTGACAA
CATGCGACCGTGA (SEQ ID NO:4).

13. Method according to one of claims 5 to 12, characterised in that the DNA Sequence of K2S consists of the following sequence:

TCTGAGGGAAACAGTGACTGCTACTTGGGAATGGGTCAAGCCTACC
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCCTGCCTCCCGTG
GAATTCCATGATCCTGATAGGCAAGGTTACACAGCACAGAACCCC
AGTGCCCAGGCACTGGGCTGGCAAACATAATTACTGCCGGAATC
CTGATGGGATGCCAAGGCCCTGGTGCCTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCTGCTCCACCTGCGG
CCTGAGACAGTACAGCCAGCCTCAGTTGCATCAAAGGAGGGCTC
TTCGCCGACATCGCCTCCCCACCCCTGGCAGGCTGCCATCTTGCCA
AGCACAGGAGGTGCCCGAGAGCGGTTCTGTGCGGGGGCATAC
TCATCAGCTCTGCTGGATTCTCTGCGCCACTGCTTCAGGAG
AGGTTTCCGCCCCACCACCTGACGGTGAATCTGGGAGAACATACC
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTGAAGTCGAAAAAT
ACATTGTCCATAAGGAATTGATGATGACACTTACGACAATGACAT
TGCCTGCTGCACTGAAATCGGATTGCTCCGCTGTGCCAGGAG
AGCAGCGTGGTCCGCACTGTGTGCCCTCCCCGGCGACCTGCAGC
TGGCGGACTGGACGGAGTGTGAGCTCCGGTACGGCAAGCATG
AGGCCTTGTCTCTTCTATTGGAGCGGCTGAAGGAGGCTCATGT
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTACTTAAC
AGAACAGTCACCGACAACATGCTGTGTGGAGACACTGGAGC
GGCGGGCCCCAGGCAAACITGCACGACGCCGCCAGGGCGATTGG
GGAGGCCCCCTGGTGTCTGAACGATGCCGATGACTTGGTGG
GCATCATCAGCTGGGCCCTGGCTGTGGACAGAAGGATGTCCCG
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTCTGACAA
CATGCGACCGTGA (SEQ ID NO:4).

14. DNA molecule characterized in that it is coding for:

- a) the OmpA protein or a functional derivative therof operably linked to
- b) a DNA molecule coding for a polypeptide containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein.

15. DNA molecule according to claim 14, characterized in that said DNA sequence comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGGATTGCAGTGGCACTGGCTGGTTCG
CTACCGTGGCCCAGGGGCCCTCTGAGGGAAACAGTGACTGCTACTT
TGGGAATGGGTCAAGCCTACCGTGGCACCGCACAGCCTACCGAGTCG
GGTGCCCTCCTGCCCTCCCGTGGAAATTCCATGATCCTGATAGGCAAGG
TTTACACAGCACAGAACCCCCAGTGCCAGGCACTGGCCTGGCA
AACATAATTACTGCCGAATCCTGATGGGGATGCCAAGCCCTGGT
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT
GCCCTCCTGCTCCACCTGCCCTGAGACAGTACAGCCAGCCTCAG
TTTCGCATCAAAGGAGGGCTTCGCCGACATGCCCTCCACCCCT
GGCAGGCTGCCATCTTGCCAAGCACAGGAGGTCGCCGGAGAGC
GGTTCCTGTGCCGGGCATACTCATCAGCTCCTGCTGGATTCTCT
GCCGCCACTGCTCCAGGAGAGGTTCCGCCACCACCTGACGG
TGATCTGGGAGAACATACCGGGTGGCCCTGGCAGGGAGGAGC
AGAAATTGAGTCGAAAATACATTGTCATAAGGAATTGATGA
TGACACTTACCGACAATGACATTGCGCTGTCAGCTGAAATCGGAT
TCTGCCCCGCTGTGCCAGGAGAGCAGCGTGGTCCGACTGTGTC
TCCCCCGGCCGACCTGCAAGCTGCCGGACTGGACGGAGTGTGAGCT
CTCCGGCTACCGCAAGCATGAGGCCTTGTCTCCTTCTATTGGAG
CGGCTGAAGGAGGCTATGTCAGACTGTACCCATCCAGCCGCTGCA
CATCACAACATTACTTAACAGAACAGTCACCGACAACATGCTGTG
TGCTGGAGACACTCGGAGCGGGGGCCCCAGGCAAACCTGACCGA
CGCCTGCCAGGGCGATTGGGAGGGCCCCCTGGTGTCTGAAACGAT
GGCCGCATGACTTGGTGGCATCATCAGCTGGGCTGGCTGTG
GACAGAAGGATGTCCCGGGTGTGACACAAAGGTTACCAACTACCT
AGACTGGATTGTCGACAAACATGCGACCG (SEQ ID NO:5).

16. DNA molecule according to claim 14 or 15, characterized in that said DNA sequence consists of the following sequence:

ATGAAAAAGACAGCTATCGGATTGCAGTGGACTGGCTGGTTTCG
CTACCGTGGCCAGGCAGCCTCTGAGGGAAACAGTGACTGCTACTT
TGGGAATGGGTAGCCCTACCGTGGCACAGCCTACCGAGTCG
GGTCGCTCCTGCCCTCCCGTGGAAATCCATGATCCTGATAGGCAAGG
TTAACACAGCACAGAACCCCCAGTGCACAGGACTGGGCCTGGGCA
AACATAATTACTGCCGAATCCTGATGGGATGCCAAGCCCTGGTGC
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT
GCCCTCTGCTCCACCTCGGGCTGAGACAGTACAGCCAGCCTCAG
TTTCGCATCAAAGGAGGGCTTCGCCGACATGCCCTCCCACCCCT
GGCAGGCTGCCATTTGCCAACGACAGGAGGTGCCGGAGAGC
GGTTCCGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCT
GCCGCCCACTGCTTCCAGGAGAGGTTCCGCCACCCACCTGACGG
TGATCTGGCAGAACATACCGGGTGGCCCTGGCAGGGAGGAGC
AGAAATTGAGTCGAAAATACATTGCCATAAGGAATTGATG
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT
TCGGTCCCCTGTGCCCCAGGAGAGCAGCGTGGTCCGACTGTG
TTCGGGCTACGGCAAGCATGAGGCCCTGCTCTTCTATTGGAG
CGGCTGAAGGAGGCTATGTCAGACTGTACCCATCCAGCGCTG
CATCACAACATTACTAACAGAACAGTCACCGACAACATGCTG
TGCTGGAGACACTGGAGCGGCGGGCCCCAGGCAAACATTG
CGGCTGCCAGGGCATTGGGAGGCCCCCTGGTGTCTGAACGAT
GGCCGCATGACTTGGTGGCATCATGAGCTGGGCTGGCTGTG
GACAGAAGGATGTCCGGGTGTGTACACAAAGGTACCAACTAC
AGACTGGATTGCGACAACATGCGACCG (SEQ ID NO:5).

17. DNA molecule according to one of claims 14 to 16, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 87 – 527 of the human tissue plasminogen activator protein.

18. DNA molecule according to one of claims 14 to 17, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 174 – 527 of the human tissue plasminogen activator protein.

19. DNA molecule according to any one of claims 14 to 18, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 180 – 527 of the human tissue plasminogen activator protein.

20. DNA molecule according to any one of claims 14 to 19, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 220 – 527 of the human tissue plasminogen activator protein.

21. DNA molecule according to any one of claims 14 to 20, characterized in that said DNA sequence a) is hybridizing under stringent conditions to the following sequence:

ATAAAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTCG
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:6).

22. DNA molecule according to any one of claims 14 to 21, characterized in that said DNA sequence a) consists of the following sequence:

ATAAAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTCG
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:6).

23. DNA molecule according to any one of claims 14 to 22, characterized in that said DNA sequence b) is hybridizing under stringent conditions to the following sequence:

TCTGAGGGAAACAGTGACTTGCTACTTGGGAATGGGTCAAGCCTACC
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG
GAATTCCATGATCCTGATAAGGCAAGGTTACACAGCACAGAACCCC

AGTGCCCAGGCCTGGGAAACATAATTACTGCCGGAATC
CTGATGGGATGCCAAGCCCTGGTGCACGTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCACCTGCGG
CCTGAGACAGTACAGCCAGCCTCAGTTGCATCAAAGGAGGGCTC
TTCGCCACATGCCCTCCACCCCTGGCAGGCTGCCATCTTGCA
AGCACAGGAGGTCGCCGGAGAGCGGTTCTGTGCGGGGGCATAC
TCATCAGCTCTGCTGGATTCTCTGCCCCACTGCTCCAGGAG
AGGTTCCGCCACCACCTGACGGTATCTGGGAGAACATACC
GGGTGGCCCTGGCAGGAGGAGCAGAAATTGAAGTCGAAAAAT
ACATTGTCATAAGGAATTGATGATGACACTTACGACAATGACAT
TGCCTGCTGAGCTGAAATCGGATTGCTCCGCTGTGCCCAGGAG
ACGAGCGTGGTCCGACTGTGCTTCCCCGGGACCTGCAGC
TGGGGACTGGACGGAGTGTGAGCTCTCCGGTACGGCAAGCATG
AGGCCTGTCTCTTCTATTGGAGCGCTGAAGGAGGCTCATGT
CAGACTGTACCCATCCAGCCGTGACATCACAACATTACTTAAC
AGAACAGTCACCGACAACATGCTGTGCTGGAGACACTCGGAGC
GGCGGGCCCCCAGGCAAACACTGACGACGCCGTGCCAGGGCGATTG
GGAGGCCCCCTGGTGTGCTGAACGATGCCGCATGACTTGGTGG
GCATCATCAGCTGGGCCCTGGCTGTGGACAGAAGGATGTCCCG
GTGTGTACACAAAGGTACCAACTACCTAGACTGGATTGTCGTGACAA
CATGCGACCGTGA (SEQ ID NO:7).

24. DNA molecule according to any one of claims 14 to 23, characterized in that said DNA sequence b) consists of the following sequence:

TCTGAGGGAAACAGTGAATGCTACTTTGGGAATGGGTCA
GCCCTACGGCACAGCCTCACCGAGTCGGTGCTCCTGCC
GAATTCCATGATCCTGATAGGCAAGGTTACACAGCACAGAAC
CCAGTGCCTGGCAGGACTGGGCCCTGGGAAACATAATTACTGCC
GGAATGGGATGCCAAGCCCTGGTGCACGTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCACCTGCGG

CCTGAGACAGTACAGCCAGCCTCAGTTGCATCAAAGGAGGGCTC
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTGCCA
AGCACAGGAGGTGCCCCGGAGAGCGGTTCTGTGCGGGGGCATAC
TCATCAGCTCCTGCTGGATTCTCTGCCGCCACTGCTCCAGGAG
AGGTTCCGCCACCACCTGACGGTGTCTGGCAGAACATACC
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTGAAGTCGAAAAT
ACATTGTCCATAAGGAATTGATGATGACACTTACGACAATGACAT
TGCCTGCTGAGCTGAAATCGGATTGCTGCCGCTGTGCCCAGGAG
AGCAGCGTGGTCCGCACTGTGTGCCCTCCCCGGCGACCTGAGC
TGCGGACTGGACGGAGTGTGAGCTCCGGCTACGGCAAGCATG
AGGCCCTGTCTCCTTCTATTGGAGCGCTGAAGGAGGCTCATGT
CAGACTGTACCCATCCAGCCGTGACATCACAACATTACITAAC
AGAACAGTCACCGACAACATGCTGTGCTGGAGACACTCGGAGC
GGCGGGCCCCAGGAAACTGACGACCCGCCAGGGCGATTG
GGAGGCCCCCTGGTGTCTGAACGATGGCCGATGACTTTGGTGG
GCATCATCAGCTGGGGCCTGGCTGTGGACAGAAGGATGCCCCG
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTGTCGTGACAA
CATGCGACCGTG (SEQ ID NO:7).

25. Fusion protein of OmpA and K2S, characterised in that it comprises a protein characterized by the following amino acid sequence or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative or a glycosylation variant thereof:

MKKTAIAIAVALAGFATVAQAASEGNSDCYFGNGSAYRGTHSLTESG
ASCLPWNSMILIGKVYTAQNPSAQALGLGKHNCRNPDGDAKPWCH
VLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQA
AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHILTVLGRTY
RVVPGEEEQKFVEKYIVHKEFDDTDYDNDIALLQLKSDSSRCQESS
VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP
SSRCTSQHLLNRVTDNMLCAGDTRSGGPQANLHDACQGDSGGPLVC

LNDGRMTLVGIISWGLGCGQKDVGPGVYTKVTNYLDWIRDNM RPG
(SEQ ID NO:8).

26. Fusion protein of OmpA and K2S according to claim 25, characterised in that it consists of a protein characterized by the following amino acid sequence:

MKTKTAAIAVALAGFATVAQAASEGNSDCYFGNGSAYRGTHSLTESG
ASCLPWNMSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAKPWCH
VLKNRRLTWYEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQA
AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHILTVLGRTY
RVVPGEQQKFEVEKYIVHKEFDDDTYDNDIALLQLKS DSSRCAQESS
VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP
SSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSGGPLVC
LNDGRMTLVGIISWGLGCGQKDVGPGVYTKVTNYLDWIRDNM RPG
(SEQ ID NO:8).

27. K2S protein, characterised in that it comprises a protein defined by the sequence SEGN (SEQ ID NO:9) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant therof.

28. K2S protein according to claim 27, characterised in that it comprises a protein defined by the sequence SEGN SD (SEQ ID NO:10) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant therof.

29. K2S protein according to claim 28 or 29, characterised in that it comprises a protein characterized by the following amino acid sequence or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative or a glycosylation variant therof:

SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA
QALGLGKHNYCRNPDPGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI
LSAAHCFQERFPFPHLTVLGRTYRVVPGEQQKFEVEKYIVHKEFDD
DTYDNDIALLQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG
YGKHEALSPFYSERLKEAHVRVLYPSSRCTSQHLLNRTVDNMLCAGD
TRSGGPQANLHDACQGDGGPLVCLNDGRMTLVGIISWGLGCGQKD
VPGVYTKVTNYLDWIRDNMRP* (SEQ ID NO:11).

30. K2S according to any one of claims 27 to 30, characterised in that it consists of a protein characterized by the following amino acid sequence:

SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA
QALGLGKHNYCRNPDPGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI
LSAAHCFQERFPFPHLTVLGRTYRVVPGEQQKFEVEKYIVHKEFDD
DTYDNDIALLQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG
YGKHEALSPFYSERLKEAHVRVLYPSSRCTSQHLLNRTVDNMLCAGD
TRSGGPQANLHDACQGDGGPLVCLNDGRMTLVGIISWGLGCGQKD
VPGVYTKVTNYLDWIRDNMRP* (SEQ ID NO:11).

31. A vector containing a DNA sequence according to any one of claims 14 to 24.

32. A vector according to claim 31, wherein said DNA sequence is preceded by a lac promoter and a ribosomal binding site.

33. The vector pComb3HSS containing a DNA according to any one of claims 14 to 24, wherein the expression of the gp III protein is suppressed or inhibited by deleting the DNA molecule encoding said gp III protein or by a stop codon between the gene coding for a polypeptide

containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein and the protein III gene.

34. A prokaryotic host cell comprising a DNA molecule according to any one of claims 14 to 24.

35. A prokaryotic host cell comprising a vector according to any one of claims 31 to 33.

36. An *E. coli* host cell comprising a DNA molecule according to any one of claims 14 to 24.

37. An *E. coli* host cell comprising a vector according to any one of claims 31 to 33.

38. Use of a DNA molecule according to any one of claims 14 to 24 or of a vector according to any one of claims 31 to 33 or a host cell according to any one of claims 34 to 37 in a method for the production of a polypeptide having the activity of tissue plasminogen activator.

39. Use according to claim 38, wherein said method is a method according to any one of claims 1 to 13.